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10/511,693	10/14/2004	Masayuki Amagai	4439-4026	9184

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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 08/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/511,693	AMAGAI ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-9,12,13,15,16,26 and 34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-9,12,13,15,16,26 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/14/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed June 5, 2006 has been received and entered. Claims 1, 8, 9, have been amended, while claims 5, 10-11, 14, 17-25, 27-33 and 35-41 have been canceled.

Election/Restrictions

Applicant's election with traverse of the invention of group IV (claims 1-41) filed June 5, 2006 is acknowledged. The traversal is on the grounds(s) that Examiner has not set forth convincing argument that the search and examination of other groups necessarily represents an undue burden for the examiner. Applicants' argument of examining all groups with the elected group is found persuasive in part. Upon review of the claims and specification, Examiner agrees that it would not be undue burden to examine all groups together. Accordingly, the restriction requirement is withdrawn.

Claims 1-4, 6-9, 12, 13, 15-16, 26 and 34 are under consideration.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered. In the instant case, applicants have

cited multiple references in the specification but they have not been considered by the Examiner as no copy of any of the publication was provided.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-9, 12, 13, 15-16, 26 and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims are drawn to a remedy to be used in gene therapy of genetic diseases comprising an immunosuppressive agent and a gene delivered in a form of naked DNA or in a liposome subsumption form. Subsequent claims limit the immunosuppressive agent to include an active ingredient that inhibits the interaction between a CD40 receptor ligand, CD40L, and a CD40 receptor on the surface of antigen presenting cells. Claim 6 limits the genetic disease to include a recessive genetic disease, subsequently limiting to an autosomal recessive genetic disease. Claims 8-9, 26and 34 are directed to a method for treating genetic disease according to remedy of claims 1-3.

It is emphasized that although claims 1-4, 6-7 12, 13 and 15-16 in part simply are products, they recite and encompass a remedy to be used for gene therapy of genetic

disease. Therefore, they have also been analyzed for their intended use in the treatment of plurality or genetic disorder more specifically autosomal recessive disease. This analysis is based on the fact that remedy for a disease, would only result in a positive outcome in the treatment of genetic disorder.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working example are not disclosed in the specification, therefore enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore, skepticism raised in enablement rejections are those raised in the art by artisan of expertise.

The aspects considered broad are: remedy to be used in gene therapy to treat any genetic disorder subsequently limiting to plurality of autosomal recessive genetic disease, any route of administration, any immunosuppressive agent subsequently limiting active ingredient an antagonist which inhibits the interaction between a CD40 receptor ligand, CD40L, any route and method of administering naked DNA or liposome.

It is noted that as instantly recited, claimed invention reads on broad genera of gene therapy by delivering composition comprising a polynucleotide for correcting a deficient gene responsible for genetic diseases into a subject is generally not enabling due to problems with, *inter alia*, targeting and expression of transgene at effective level by naked DNA or liposome to elicit therapeutic effective response. The specification fails to provide an enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance as to how an artisan of skill would have practiced the claimed remedy and method in expressing any gene at any levels in any subject administered via any route for the treatment of any genetic disorder. An artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because art of gene delivery *in vivo* by naked DNA /liposome is unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced in any subject. As will be shown below, broad aspects were not enabled for the claimed invention at the time of filing of this application because neither the specification nor the art of record taught sufficient

guidance to practice the claimed invention. For purposes to be shown in the state of the prior art, the question of lack of enablement is discussed.

As a first issue, the claims 1-4, 6-9, 12, 13, 15-16, 26 and 34 are broad and embrace remedy to be used in gene therapy of any genetic diseases comprising an immuno-suppressive agent and delivering a naked DNA of gene responsible for genetic diseases by any route. The specification teaches that plasmid vector based gene transfer methods could be used to correct nucleic acids encoding the desmoglein (dsg) (see page 16, lines 4-15 of the specification). The specification further teaches an expression vector using CMV promoter (plasmid pcDNA: mDsg3), which is injected into Dsg3-/- mouse superficial dermis (example 1). It is noted that immuno fluorescence staining shows the expression of MDsg3 expression between epidermal cells of pcDNA: mDsg3-introduced site 18 hours after the injection of plasmid DNA (Figure 1a, example 1). However, the specification has provided no working example showing that disclosed remedy could be expressed at sustained levels by administering the naked DNA/liposome to any site by any method. Prior to instant invention, the art teaches a remedy for any genetic disorder involving plasmid DNA or liposome for correcting the deficiency of the gene was not predictable. The state of the prior art with respect to delivery of naked plasmid DNA effectively summarized by the reference of Niidome et al. (Gene Ther. 2002, 9(24): 1647-52) note: "owing to rapid degradation by nucleases in the serum and clearance by the mononuclear phagocyte system, the expression level and the area after injection of naked DNA are generally limited." (Column 1, page 1648). The authors conclude "we are far from the perfect gene carrier suitable for use. ..."we

are still relatively ignorant about factors controlling the stability, pharmacokinetics and bio-distribution of non-viral vectors. Much of the above effort has been carried out in rodents and whether the new improvements are applicable to larger animals remains to be seen. We are still far from the perfect gene carrier suitable for clinical use, and much more work is still ahead of us" (paragraph 1, p. 1651). This assertion is further supported by non-uniform and poor expression of TGase1 gene after direct injection (Choate et al Hum Gene Ther. 1997;8(14): 1659-65). It is further noted that, direct injection failed to correct the central histological and functional abnormalities of the disease suggesting that only partial restoration of gene expression can be achieved via direct injection of naked DNA in human genetic skin disease tissue (see abstract). It is evident from the cited art that the administration of plasmid DNA encoding any gene for correcting deficient gene for genetic disease by delivering naked DNA or liposome is not routine and remain unproven and unpredictable.

As a second issue, the scope of invention as claimed encompasses a remedy to be used in gene therapy of any genetic disease comprising administering any immunosuppressive agent. Subsequent claims limit the remedy to include an antagonist that inhibits the interaction between a CD40 receptor ligand, CD40L, and a CD40 receptor on the surface of antigen presenting cells. The specification contemplates plurality of immunosuppressive including Cyclosporin A, tacrolimus (FK506), Cyclophosphamide, azathioprine, mizoribine, steroid, Methotrexate, antihistamine and others such as antibody against CD40L (see page 13, para 1). The specification also teaches that naked DNA injection in Dsg3-/- mice resulted in anti-Dsg3 IgG antibody in

the serum (see example 2, Figure 2). It is noted that the imunne responses against a desmoglein 3 (Dsg3) in a DSG3 knockout mouse can be prevented by blocking the co-stimulatory interaction of CD40 on APC with CD40L on CD4+ T-helper cells (example 3-5). However, induction and maintenance of substaintial tolerance is frequently difficult to achieve, and remains an area of active investigation. The specification discloses blocking the necessary costimulation between CD40 and CD40L with a monoclonal antibody that is specific for CD40L. The guidance provided by the specification amounts to an invitation for the skilled Artisan to try and follow the disclosed instructions to make and use the claimed invention. Furthermore, Miller et al (Transfus Med Hemother 2005; 32:322–331 & Transplantation, 2001, 72(8), S5-S9) while reviewing the state of immune tolerance describe it to be a "multi-step process, which is also induced by a great variety of mechanisms influencing both T and B cells and their precursors. A defect in one of the many genes that control the development and function of self-reactive T or B cells can lead to a plethora of autoimmune conditions. Devising ways to influence some of these genes may possibly yield practical results. Miller further asserts" although immunological tolerance was first proven experimentally in 1953, more than half a century later we are still unable to induce effective and long lasting specific tolerance in transplantation" (see page 331). It is unclear from the specification that how B-cell tolerance correlates with T-cell tolerance as described in instnat application. Furthermore, Reipert et al (Throm Hemost, 2001, 86, 1345-1352) while studying the role of CD40/CD40L interaction in immune tolerance conclude "that the blockade of CD40/CD40L interactions during the treatment of hemophilic E-17 mice with human

FVIII completely prevents the development of anti-FVIII antibodies and suppresses the induction of FVIII-specific T cells. The initial blockade of costimulatory interactions is, however, obviously not sufficient to induce a lasting immune tolerance against FVIII. The initial immune suppression is abolished after the omission of the blocking anti-CD40L antibody in subsequent challenges with FVIII. It is apparent that each method of immuno suppression requires further experimentation that is not routine and subject to variation in physiological results. Thus, it is clear without any specific guidance on regulation of immune system and merely relying of CD40L antagonism is not enabling, because of the art, as shown above, does not disclose how B cell would correlate with T cell and how CD40 antagonism could results in sustained immune tolerance that is required for repeated dosing of naked DNA. Artisan could not predict, in the absence of proof to the contrary, that such a method would be efficacious in maintaining sustained immune tolerance. An artisan would have to carry out extensive experimentation to make use the invention, and such experimentation would have been undue because of the art of lasting immune tolerance is unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced.

As a third issue claims 1-4, 6-9, 12, 13, 15-16, 26 and 34 embrace introducing a nucleic acid encoding a polypeptide via any route of administration (i.e oral, intranasal, intramuscular, intravenous, subcutaneous etc.). It has been difficult to predict the efficacy and outcome of transduced therapeutic gene because several factors govern the expression and/or therapeutic potential of transduced gene *in vivo*. The transduction of target cells represent the first critical step in any gene based therapy, which not only

depends upon the type of target cells but also on the choice and/or characteristics of delivery vehicle. In addition, besides the limitations in gene transfer the problem to selectively target cells *in vivo* is still one of the most difficult obstacles to overcome (as discussed before, *supra*). For example, upon systemic administration the non-viral particle may bind to many cells they encounter *in vivo* and therefore would be diluted before reaching their targets. Besides direct administration into skin, the specification provides no other specifics or showing that other routes of administration would result in expression in skin or other organs for the treatment of plurality of genetic disorder. The specification fails to provide an enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance as to how an artisan of skill would have practiced the claimed method in human by administering claimed compositions via any route. An artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because art of the gene delivery was not routine rather it was unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced.

As a final issue, the claims 1-4 and 8, embrace a remedy to be used in gene therapy of genetic disease and a method for treating genetic disease more specifically autosomal recessive genetic disease. The specification contemplates remedy for a number of disease including pemphigus, recessive genetic epidermolysis bullosa hereditaria dystrophica, junctional epidermolysis bullosa hereditaria, hemidesmosome epidermolysis bullosa hereditaria, ichthyosis congenita, albinism, Tay-Sachs disease, Wilson disease, Cystic Fibrosis, Phenylketonuria, type I glycogenosis, galactosemia.

Examples of sex-linked genetic diseases include achromatopsia, hemophilia A, Duchenne type muscular dystrophy to name few. In addition, it is noted that specification teaches introducing desmoglein by injection to demonstrate transient expression of dsg at the site of injection. The specification also describes a grafting a wild type skin that expresses a normal Dsg3 protein onto a Dsg3-/- knockout lacking Dsg3. It is noted that this transplantation experiment can be considered analogous to skin gene therapy that introduces the normal Dsg3 gene into skin where normal Dsg3 expression is lacking. It is also noted that the titers of the anti-Dsg3 antibody immune response could be reduced by costimulation blockade in animals treated with antibodies that bound CD40L (example 6). However, this disclosure does not provide sufficient guidance to an artisan to treat any genetic disorder. The instant claims read on treating any genetic disorder in any subject using the claimed remedy and method. However, it is unclear which conditions are treatable by the claimed remedy and method. Passeron et al (Clinics in Dermatology, 23(1), 2005, pp 56-67) in a post filing art disclose "127 loci are known to affect pigmentation in mouse when they are mutated". However, it is noted that the only one third of gene involved is presently identified (abstract). Passeron et al describe that Dyschromatosis symmetrica hereditaria is a very rare autosomal skin disorder characterized by the association of hypo pigmented and hyper pigmented macules mostly on the back of the hands and feet. In spite of some advances in understanding of this disorder, the pathogenesis leading to these characteristic pigmentary troubles is largely unknown (pp 65, col. 1, para 2, lines 17-21). Thus, states of art clearly suggest that many of genetic pigmentary disorder of different pathology

and etiologies involve different and distinct mechanisms that are presently not completely elucidated. It is clear that skilled artisan would require undue experimentation to practice the remedy and method as contemplated by the instant claims particularly given the unpredictability of nucleic acid therapy as whole and unpredictability expressed in the art for the gene delivering in the treatment of genetic disorder in any subject.

The cited arts clearly indicate an unpredictable status of the gene therapy art pertaining to treatment of genetic disorder by naked DNA or liposome that require sustained expression of transgene at a specific site for prolonged period of time.

In conclusion, in view of breadth of the claims and absence of a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for the claimed inventions. The specification and prior art do not teach a method of *in vivo* delivery of gene such that it is expressed at therapeutic effective level for desired duration at any sites of any subject suffering from any genetic condition. An artisan of skill would have required undue experimentation to practice the remedy and method of gene therapy. Since gene therapy is clearly unpredictable in terms of achieving desired levels of gene expression for appropriate duration to results in a therapeutic effect in correcting genetic disorder at the time of filing of this application as supported by the observations in the prior art.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 6-8, 26 and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Radhakrishnan et al (WO 99/59638, dated 11/25/1999).

Claims are directed to a remedy to be used in gene therapy of genetic diseases for correcting a deficient gene comprising an immunosuppressive agent and a gene responsible for genetic diseases. Claim 6 limits the genetic disease of claims 1-2 to include recessive genetic disease, subsequently limiting to autosomal recessive genetic disease. Claim 8 is directed to a method of treating genetic disease comprising administering a remedy comprising the remedy of claims 1 and 2. Subsequent claims limit the genetic disease to include autosomal recessive disease.

Radhakrishnan et al teach composition and method for the delivery of nucleic acid *in vivo* to cells (abstract, example 1). It is noted that Radhakrishnan contemplated a wide array of nucleic acid molecule in a vector to direct expression of a protein including nucleic acid encoding Factor VIII and IX and immunomodulatory co-factors. The nucleic acid molecule comprising immunomodulatory co factors includes those molecules that can either increase or decrease the recognition, presentation or activation of either cell mediated or humoral immune response (see page 9, line 13-15). In addition, Radhakrishanan also includes those sequences that encode protein required to replace

a normal gene function capable for stabilizing or reversing inherited or non inherited genetic disease such as CFTR, factor VIII and IX (see page 9- lines 27 –32 bridging o page 10, lines 1-12). It is emphasized that Radhakrishnan also contemplates vector may direct the expression of at least two different recombinant or synthetic nucleic acid molecule such as immunomodulatory and therapeutic transgene (see page 3 lines 15-30), thus meeting the claim limitation of claim 1-2 and 6-7. It is noted that the method of independent claim, claim 8 recite one steps: (a) administering a immunosuppressive agent and gene correcting the deficient gene. The cite art teach same method step of administering a naked DNAin mouse TA muscle (see figure 1). Since, Radhakrishnan contemplated administering one or more nucleic acid. Accordingly, the invention of claims 8, 26 and 34 would be anticipated by Radhakrishnan because steps recited in the invention are the same as those taught by the cited arts.

Thus, cited art clearly anticipate claims 1-2, 6-8, 26 and 34.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-4, 6-8,12, 13, 15-16, 26 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dwarki et al (WO 99/06562 dated 2/11/1999, IDS); Radhakrishnan et al (WO 99/59638, dated 11/25/1999) and Takahama et al (EP 1142473, dated 10/10/2001, IDS).

Dwarki et al teach administering a patient replication defective adeno associated virus comprising a gene encoding a Factor VIII or IX or Xa and an immunosuppressant that suppresses the patients humoral immune response (abstract). It is known in the art that deficiencies of coagulation factors other than factor VIII and factor IX such as factor X that cause bleeding disorders are inherited as autosomal recessive traits. Thus, Dwarki teaches administering nucleic acid encoding protein directed to correct deficiency of X-linked genetic disease as well as rare autosomal recessive bleeding disorder by providing cofactor for Factor X. Dwarki contemplates vector could be any genetic element that is capable of replication and that could transfer DNA or RNA sequence between cells including plasmid, phage and cosmid (page 11, lines 7-11). Further, Dwarki et al also teach administering a humoral immunosuppressant including antiCD40L antibody with therapeutic gene (claim 3, 21 and 23). It is noted that immune response is to protein produces as well as to the vector administration. Dwarki et al differ from claimed invention by suggesting using an AAV instead of naked DNA or liposome.

Radhakrishnan et al teach composition and method for the delivery of nucleic acid *in vivo* to cells (abstract, example 1). It is noted that Radhakrishnan contemplated a wide array of nucleic acid molecule in a vector to direct expression of a protein including nucleic acid encoding Factor VIII and IX and immunomodulatory co-factors. The nucleic acid molecule comprising immunomodulatory co factors includes those molecules that can either increase or decrease the recognition, presentation or activation of either cell mediated or humoral immune response (see page 9, line 13-15). In addition, Radhakrishanan also includes those sequences that encode protein required to replace a normal gene function capable for stabilizing or reversing inherited autosomal recessive genetic disease such as CFTR and factor VIII or IX (see page 9- lines 27 –32 bridging o page 10, lines 1-12). It is emphasized that Radhakrishnan also contemplates vector may direct the expression of at least two different recombinant or synthetic nucleic acid molecule such as immunomodulatory and therapeutic transgene (see page 3 lines 15-30), thus meeting the claim limitation of claim 1-2 and 6-7. However, Radhakrishnan et al do not teach administering an antagonist that inhibits the interaction between a CD40 receptor ligand.

Prior to instant invention, Takahama et al teach a method for acquiring immunological tolerance to a foreign DNA such as a vector carrying a foreign gene that is useful for genetic disease therapy (column 3, lines 26-30, paragraph 8). Takahama discloses various methods in prior art for acquiring immunological tolerance (see column 2, lines 26-54). However, Takahama et al do not teach administering an antagonist that inhibits the interaction between a CD40 receptor ligand.

It would have been obvious for one of ordinary skill in the art at the time of invention to modify the delivery method of remedy disclosed by Dwarki et al to include naked DNA/plasmid taught by Radhakrishnan. It is noted that Radhakrishnan had already disclosed that an immunomodulatory gene could be administered along with therapeutic gene. In addition, Takahama provided motivation by suggesting that immunological tolerance could be achieved to foreign DNA or its expression product, while Radhakrishnan disclosed composition to decrease the recognition, presentation or activation of either cell mediated or humoral immune response. Thus, skilled artisan would have been motivated to modify its remedy to be used in gene therapy by delivering the remedy as naked DNA or as liposome as taught by Radhakrishnan, as it would have elicited lesser immune response to the delivery vehicle and it was already shown that plasmid with plurality of therapeutic gene would have resulted in sustained stable expression of transgene.

One who would practiced the invention would have had reasonable expectation of success because Dwarki and Radhakrishnan had already described a remedy for gene therapy for disease like CFTR, factor VIII and factor Xa by correcting deficient gene responsible in conjunction with a immunomodulatory gene. It would have only required routine experimentation to deliver gene as naked DNA/plasmid that was disclosed by Radhakrishnan before filing of this application. One of ordinary skill in art would have been motivated to combine the teaching of Dwarki, Radhakrishnan and Takahama because a remedy comprising a gene correcting a deficient gene and

immunosuppressant like CD40L antibody would have provided deficient gene in the subject for the treatment for genetic disorder.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Claims 1-4, 6-9, 12, 13, 15-16, 26 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dwarki (WO99/06562 dated 2/11/1999, IDS); Radhakrishnan et al (WO99/59638, dated 11/25/1999), Takahama et al (EP 1142473, dated 10/10/2001, IDS) and Chen et al (Journal of Biological Chem., 275, 32 24429-24435).

The combined teachings of Dwarki, Radhakrishnan and Takahama have been discussed above and are relied upon in same manner. However, none of the references explicitly teaches providing gene for correcting recessive epidermolysis bullosa.

Prior to instant invention, Chen et al disclose dystrophic epidermolysis bullosa (DEB) is an inherited mechano-bullous disorder of skin caused by mutations in the type VII collagen gene (abstract). Chen et al teach minigene product, a truncated type VII collagen α chain which retained the function and characteristics of a full-length type VII collagen α chain showed expression of minicollagen VII in RDEB keratinocytes reversed the RDEB cellular phenotype (see page 24430. column 1, paragraph 3 and page 24432, column 1, paragraph 3 and figure 6-8). It is noted that Chen et al demonstrated successful correction of gene-deficient human keratinocytes *in vitro* and contemplates these results as basis for future *ex vivo* gene therapy for DEB (see page 24435, column

1, last paragraph). However, Chen et al do not specifically teach administering naked DNA for correcting the deficiency.

It would have been obvious for one of ordinary skill in the art at the time of invention to modify the delivery method of remedy disclosed by Dwarki et al to include naked DNA/plasmid taught by Radhakrishnan. It is noted that Radhakrishnan had already disclosed that an immunomodulatory gene could be administered along with therapeutic gene. In addition, skilled artisan would have been further motivated to include truncated type VII collagen α chain for the treatment of dystrophic epidermolysis bullosa because Chen had already showed successful correction of gene-deficiency *in vitro*. Takahama provided motivation by suggesting that immunological tolerance could be achieved to foreign DNA or its expression product, while Radhakrishnan disclosed composition to decrease the recognition, presentation or activation of either cell mediated or humoral immune response. Thus, skilled artisan would have been motivated to modify its remedy to be used in gene therapy by delivering truncated type VII collagen α chain as naked DNA as taught by Radhakrishnan, as it would have elicited lesser immune response and it was already shown that plasmid with plurality of therapeutic gene would have resulted in sustained stable expression of transgene.

One who would practiced the invention would have had reasonable expectation of success because Chen had already described that truncated type VII collagen α chain reversed the RDBE cellular phenotype by correcting deficient gene. It would have only required routine experimentation to deliver gene as naked DNA/plasmid that was disclosed by Radhakrishnan before filing of this application. One of ordinary skill in art

would have been motivated to combine the teaching of Chen, Dwarki, Radhakrishnan and Takahama because a remedy comprising a gene correcting a deficient gene and immunosuppressant like CD40L antibody would have provided successful treatment of dystrophic epidermolysis bullosa (DEB).

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

No claims allowed.
The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Jiang et al. Animal models of epidermolysis bullosa--targets for gene therapy. J Invest Dermatol. 2005; 124(3):xi-xiii.

Jiang et al reviews the progress made in developing animal models for epidermolysis bullosa. Jiang et al further discussed several transgenic animal models and suggest these models provide basis for gene therapy approach. The goal of the teachings of Jiang et al appeared to be usefulness of transgenic mice in studying the role of genetic disorder and their potential use in gene therapy application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM- 5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272- 0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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